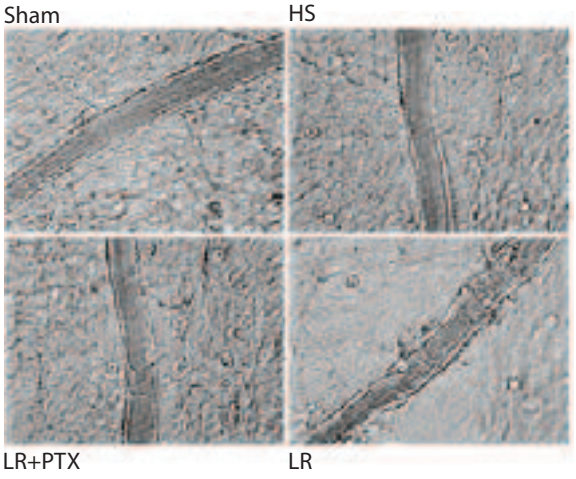
MECHANISMS OF HYPERTONIC SALINE SOLUTION ASSOCIATED TO PENTOXIFYLLINE AND ETHY-PYRUVATE IN THE REDUCTION OF MULTIPLE ORGAN DYSFUNCTION AFTER TRAUMA, SEPSIS AND ISCHEMIA-REPERFUSION

Maurício Rocha e SILVA

Heart Institute (InCor)



Representative image of intravitral microscopy of the spermatic fascia vasculature 2 hrs after shock and fluid resuscitation. No adherent cells were seen in the sham group. Lacted Ringer's (LR) plus pentoxifylline (Lr+PTX) and hypertonic saline (HS) treated animals had a very similar number of adherent polymorphonuclear leukocytes (PMN), which were markedly fewer than in LR-treated animals. (Yada-Langui et al. 2004)

Our goal is to investigate the mechanisms by which hypertonic saline solution, associated to pentoxifylline and ethyl-piruvate may attenuate multiple organ dysfunction after trauma, sepsis and ischemia-reperfusion, a major health worldwide problem due to its prevalence and to the high associated morbidity and mortality. We are testing the hypothesis that hypertonic saline solution, associated to pentoxifylline, ethyl-piruvate used in the treatment of hemorrhagic or septic shock, and ischemia-reperfusion of large territories induced by surgical maneuvers, decrease multiple organ dysfunction due to its beneficial effects would be particularly in the hepatosplanchnic area, through hemodynamic improvement at the macro and microcirculatory levels, by reducing ischemia-reperfusion injury and systemic inflammatory response, and preserving cellular function. We are employing clinically relevant experimental models of uncontrolled hemorrhagy, sepsis by live bacteria infection and peritonitis, and ischemia-reperfusion induced by surgical maneuvers, to evaluate the systemic and regional hemodynamic effects and the mechanisms by which such solutions may reduce multiple organ dysfunction in pigs and rats. Complex organ function monitored for a long period and the maintenance of these animals, in a facility similar to intensive care units, is a critical step before testing the potential clinical use of those solutions. In parallel, studies in small animal models of hemorrhage, sepsis and ischemia-reperfusion are being conducted, addressing important aspects of the microcirculatory, cellular and inflammatory effects of those solutions, which remains to be understood.

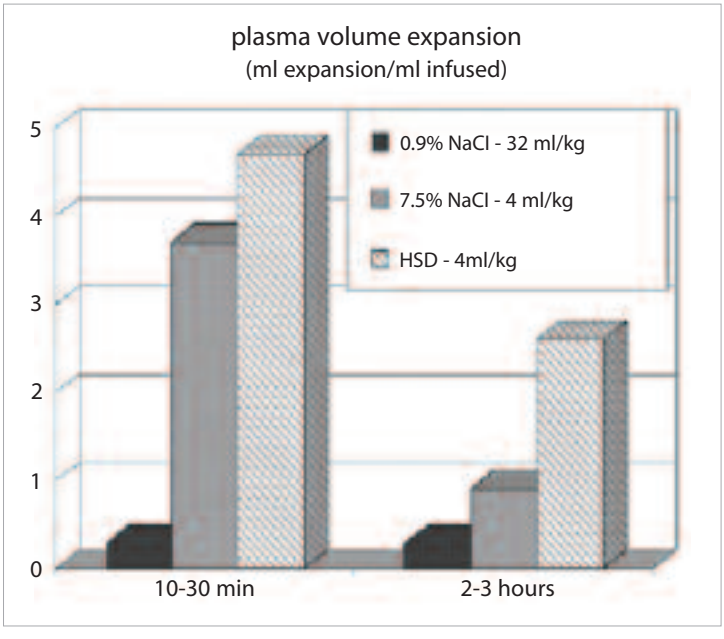
SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Our results in large and small animal models of hemorrhagy, sepsis and ischemia-reperfusion are confirming our hypothesis that hypertonic saline and pentoxiffiline have potent synergistic beneficial effects, reducing organ damage, largely due to microcirculatory and cellular mechanisms.

Our treatment have reduced endothelial-leukocyte interaction, inflammation, organ dysfunction and apoptosis in uncontrolled hemorrhagy, sepsis due to live bacteria injection or cecal-ligation and puncture, and ischemia-reperfusion after aortic or mesenteric artery occlusion.

Our most striking observation is that all those microcirculatory and cellular benefits have been achieved in a small-volume resuscitation regimen with hypertonic-pentoxifilline, which promotes similar plasma expansion, and systemic and regional hemodynamic benefits as large volume crystalloids (8 times greater volume), the actual standard of care in the management of trauma victims, septic and surgical patients. The potential for clinical trials testing these hypothesis are real.

Plasma volume expansion in ml expansion per ml infused after 32 ml/kg isotonic NaCl, 4 ml/kg 7.5% NaCl, or 4 ml/kg 7.5% NaCl-6%Dextran-70



MAIN PUBLICATIONS

Yada-Langui MM, Anjos-Valotta EA, Sannomiya P, Rocha e Silva M, Coimbra R. 2004. Resuscitation affects microcirculatory polymorphonuclear leukocyte behavior after hemorrhagic shock: role of hypertonic saline and pentoxifylline. *Exp. Biol. Med.* **229**:684-693.

Rocha e Silva M, Poli de Figueiredo LF. 2005. Small volume resuscitation of circulatory shock. *Clinics*. **60(2)**:163-178.

Poli de Figueiredo LF, Cruz Jr RJ, Yada-Langui M, Rocha e Silva M. 2005. Sustained gastric mucosal acidosis in spite of rapid global and regional hemodynamic restoration after hemorrhage and resuscitation with blood or hypertonic/hyperoncotic solution. *Journal of Investigative Surgery*. **18**:257-264.

Cruz Jr RJ, Yada-Langui MM, Poli de Figueiredo LF, Sinosaki S, Rocha e Silva M. 2006. Synergistic effects of pentoxifylline on systemic and regional perfusion after hemorrhage and hypertonic resuscitation. *Anesthesia & Analgesia*. **102**:1518-1524.

Nakagawa NK, Nogueira RA, Correia CJ, Shiwa SR, et al. 2006. Leukocyte-endothelium interactions after hemorrhagic shock/reperfusion and cecal ligation/puncture: an intravital microscopic study in rat mesentery. *Shock*. **26**:180-186.

Garrido AG, Cruz Jr RJ, Poli de Figueiredo LF, Rocha e Silva M. 2006. Small volume of hypertonic saline as the initial fluid replacement in experimental hypodynamic sepsis. *Critical Care*. **10(R62)**:1-9.

Pinto FCG, Capone Neto A, Prist R, Rocha e Silva M, Poli de Figueiredo LF. 2006. Volume replacement with lactated Ringers or 3% hypertonic saline solution during combined experimental hemorrhagic shock and traumatic brain injury. *Journal of Trauma*. **60**:758-764.

Nakagawa NK, Jukemura J, Aikawa P, et al. 2007. *In vivo* observation of mesenteric leukocyte-endothelial interactions after cecal ligation/puncture and surgical sepsis source control. *Clinics*. **62(3)**:321-326.

Rahal, Garrido AG, Cruz Jr RJ, Silva E, Poli de Figueiredo LF. 2008. Fluid replacement with hypertonic or isotonic solutions guided by mixed venous oxygen saturation in experimental hypodynamic sepsis. *Critical Care*, submitted.

Maurício Rocha e SILVA

Instituto do Coração (InCor)
Faculdade de Medicina
Universidade de São Paulo (USP)
Departamento de Cardiopneumologia
Av. Enéas de Carvalho Aguiar, 44 – Cerqueira Cesar
05403000 – São Paulo, SP – Brasil

+55-11-30695257
mrsilva36@hcnet.usp.br